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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,435	05/02/2006	Jeffrey D. Rothstein	JHU2090-1	2771

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EXAMINER	
MACFARLANE, STACEY NEE	
ART UNIT	**PAPER NUMBER**
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,435	ROTHSTEIN ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,9,10 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 9, 10 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/8/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Claim 1, 5, 6, 8, 11, 12, 18 and 20-44 have been canceled. Claim 2 has been amended as requested in the amendment filed on March 8, 2010. Following the amendment, claims 2, 9, 10 and 19 are pending in the instant application and are under examination in the instant office action.

2. Applicant's arguments filed on March 8, 2010 have been fully considered but they are not deemed to be persuasive for the reasons set forth below. Prior art was applied in so far as it read upon the limitations of the previously presented claims. In view of the current claim amendments to include the new method step of "detecting the level of glycosylation of a GTRAP3-18 target molecule", the art applied is moot.

Claim Rejections - 35 USC § 101 (Withdrawn)

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The rejection of Claims 2, 9, 10 and 19 under 35 U.S.C. 101 is withdrawn. Examiner has found evidence within the art that a naturally occurring mutation in EAAT2, which specifically reduces glycosylation of the transporter and reduces glutamate uptake, is associated with the specific neurological disorder of amyotrophic lateral sclerosis (ALS).

Claim Rejections - 35 USC § 102 (New Grounds Necessitated by Amendment)

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 2, 9 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruggiero et al., GTRAP3-18: A GENERAL REGULATOR OF EAAT ACTIVITY AND PNGASE F SENSITIVE GLYCOSYLATION, Program No. 441.11, 2002 Abstract, Society for Neuroscience, September 2002 (cited on IDS filed 3/8/2010).

6. Claims 2, 9 and 10 are drawn to a method comprising contacting a cell which expresses GTRAP3-18 with a test compound and detecting the level of glycosylation of a GTRAP3-18 target molecule, thereby identifying the test compound as a modulator of cellular glycosylation; Wherein the GTRAP3-18 target molecule is a glutamate transporter selected from the group EAAT1, EAAT2, EAAT3, EAAT4 and EAAT5.

7. The Ruggiero et al. prior art teaches "GTRAP3-18 has a physiologic effect on rEAAT3 activity and decreases its affinity for the substrate glutamate … The level of GTRAP3-18 expression determines the relative reduction in rEAAT3 activity. We have expanded our analysis of GTRAP3-18 to include other EAAT subtypes. Expression of GTRAP3-18 is able to modulate both the activity and glycosylation state of other glutamate transporters to the same extent as with rEAAT3 ... GTRAP protein may lead to an overall decrease in EAAT function in neuronal and non-neuronal cell types in response to retinoic acid and other physiologic stimuli."

8. The Ruggiero prior art explicitly teaches a method comprising contacting HEK 293 cells expressing GTRAP3-18 with a test compound, which can be either the glutamate substrate or the retinoic acid of the reference, and determining the glycosylation level of EAAT glutamate transporters. Thus, the method of the instant claims fails to distinguish over that of the prior art.

Claim Rejections - 35 USC § 103 (New Grounds Necessitated by Amendment)

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

As currently amended to include a recitation of “detecting the level of glycosylation of a GTRAP3-18 target molecule", Claims 2, 9, 10 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (2001) cited in the Office action mailed June 13, 2007, and further in view of Trotti et al. Journal of Biological Chemistry, 276(1): 576-582, 2001.

The Lin prior art teaches contacting cells expressing GTRAP3-18 with test compounds (antisense oligomers and retinoic acid) and assaying the ability of the test compounds to modulate GTRAP3-18 protein expression. Specifically, the Lin reference teaches neuronal cells and transfected cell lines contacted with retinoic acid increase GTRAP3-18 protein expression (Figure 4a). Lin et al. also demonstrate that antisense GTRAP3-18 oligomers modulate, namely reduce, endogenous GTRAP3-18 expression (Figure 3d). The Lin et al. prior art further discloses a specific protein-protein interaction between GTRAP3-18 and EAATs (Figure 1), thus, identifying these glutamate transporters as GTRAP3-18 target molecules. The Lin et al., reference further teach that the expression of GTRAP3-18 negatively modulates the activity of the transporter (Figure 3a), with increased GTRAP3-18 expression directly resulting in decreased transport activity.

The Lin reference does not teach "detecting the level of glycosylation of a GTRAP3-18 target molecule", as currently required by claim 2, part (b). However, the Trotti et al. prior art teach that it was well-known in the art at the time of filing that the glycosylation state of EAAT transporters affects glutamate clearance activity. Specifically, Trotti et al. teach that a site mutation in one of the two glycosylation sites within EAAT2 results in marked decreased activity and is associated with ALS. The Trotti reference teaches methods comprising detecting the level of glycosylation of GLT1 (a.k.a. EAAT2, see instant claim 10) by reduced molecular weight on a Western blot versus wild type, but equivalent weight with PNGase glycosidase-treated transporter. Trotti et al. also explicitly teach that defective plasma membrane targeting

was reported for other glycosylation-deficient transporters (page 581, column 2, first full paragraph).

It would have been obvious to one of ordinary skill to use the methods for detection of glycosylation level, as taught by Trotti et al., in the methods for assessing the negative modulation of EAATs by GTRAP3-18 as taught by Lin et al. A skilled artisan would have been motivated to combine the methods because the Trotti et al. art explicitly teaches that it was well recognized within the art that deficiencies in glycosylation affect transporter activity. In *KSR International Co. v. Teleflex, Inc.,* the Supreme Court has stated that combining prior art elements according to known methods to yield predictable results is *prima facie* obvious. Based upon the guidance and direction within the Trotti and Lin prior art references, such combination would have been well within the technical grasp of a skilled artisan. Since each of the methods in combination are merely performing the same function as they did separately, then one of ordinary skill in the art would have been able to predictably combine the elements with a reasonable expectation of success of determining the level of glycosylation of EAAT proteins in the presence of GTRAP3-18 and test compounds. Therefore, the invention as a whole is *prima facie obvious*.

11. As currently amended, Claims 2, 9, 10 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6808893 ('893 Patent, cited in the previous Office action) and further in view of Trotti et al. 2001 (*supra*).

The '893 Rothstein Patent teaches methods comprising contacting cells with test compounds (GTRAP3-18 antisense oligonucleotides and retinoic acid) and assaying the ability of these test compounds to reduce GTRAP3-18 protein expression. Specifically the '893 Patent that GTRAP3-18 antisense oligonucleotides decrease GTRAP3-18 protein expression (Figure 8A-C), and states, "Retinoic acid induces a large increase in GTAP3-18 expression" (column 46, lines 40-41). Furthermore, the Rothstein Patent discloses that GTRAP expression directly modulates EAAT activity (Figures 3B, 4A and 6A-C).

The '893 Patent does not teach "detecting the level of glycosylation of a GTRAP3-18 target molecule", as currently required by claim 2, part (b). However, the Trotti et al. prior art explicitly teach methods for detecting the glycosylation state of the EAAT transporters. Additionally, Trotti et al. teach that it was well-known in the art at the time of filing that the glycosylation state of EAAT transporters intimately affects transporter activity and that this was a common feature among other glycosylation-deficient transporters.

It would have been obvious to one of ordinary skill to use the methods for detection of glycosylation level, as taught by Trotti et al., in the methods for assessing the modulation of EAAT1 activity by GTRAP3-18, as taught by Lin et al. A skilled artisan would have been motivated to combine the methods because the Trotti et al. art explicitly teaches that glycosylation affects transporter activity. In *KSR International Co. v. Teleflex, Inc.,* the Supreme Court has stated that combining prior art elements according to known methods to yield predictable results is *prima facie* obvious. Based

upon the guidance and direction within the Trotti and Lin prior art references, such combination would have been well within the technical grasp of a skilled artisan. Since each of the methods in combination are merely performing the same function as they did separately, then one of ordinary skill in the art would have been able to predictably combine the elements with a reasonable expectation of success of determining the level of glycosylation of EAAT proteins in the presence of GTRAP3-18 and test compounds. Therefore, the invention as a whole is *prima facie obvious*.

Conclusion

12. No Claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M-R 5:45 to 3:30, TELEWORK-Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
June 3, 2010